Beyond the Ovary: Understanding PCOS as a Systemic Disease

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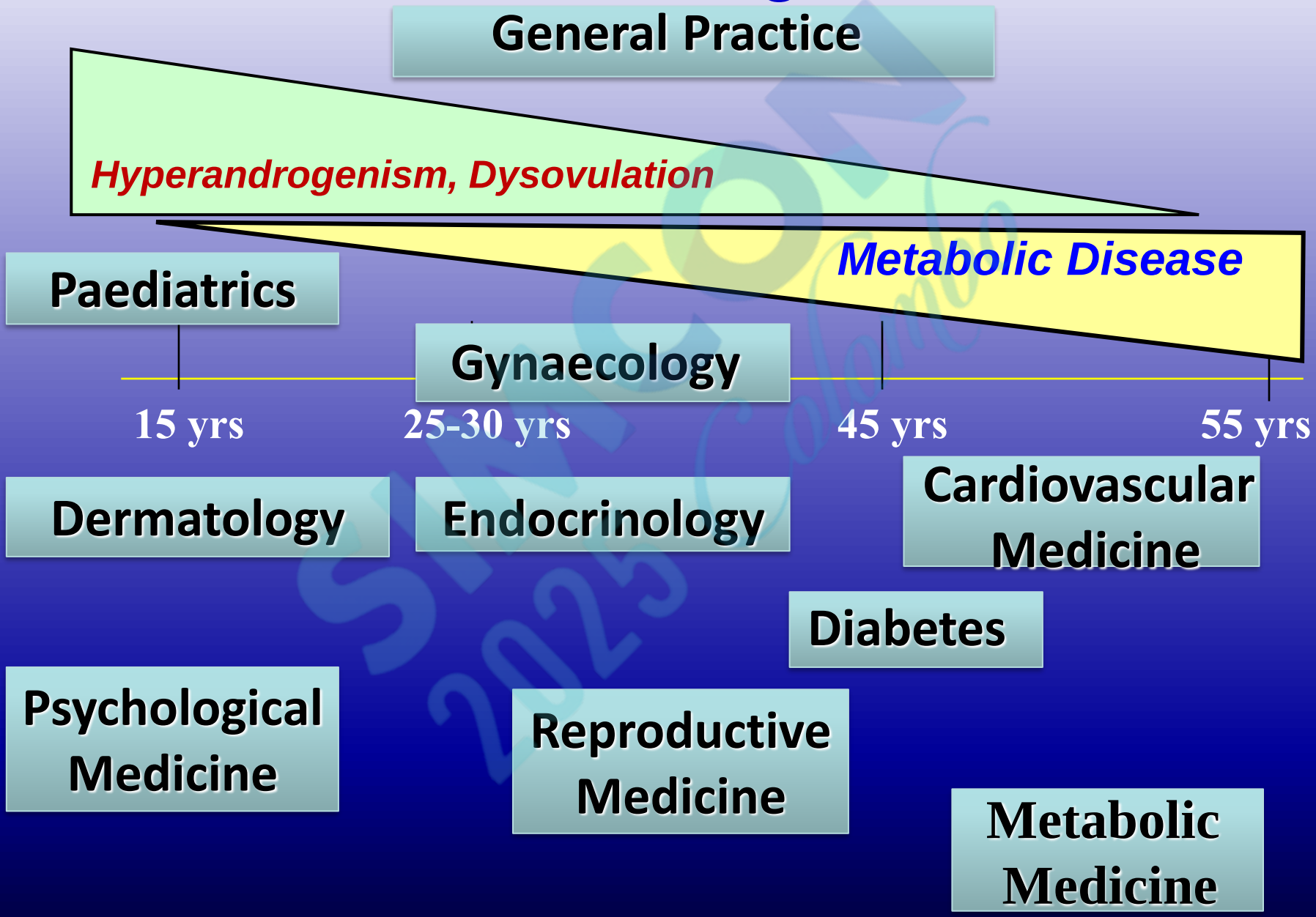
A CONDITION OF OUR TIMES

PCOS

- **Commonest endocrinopathy 08 – 13%**
- **Impacts throughout the life cycle**
- **Psycho-social issues +++**

International Guideline Development Groups, NHMRC , 2023

PCOS: a life long condition



PCOS : a life-long condition

Evolution during adolescence

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Difficult to define in post-menarche

ESHRE/ARSM consensus 2012

PCOS as a Chronic Inflammatory Disorder

Chronic Low-Grade Inflammation
Elevated cytokines and oxidative stress markers

Drives metabolic and reproductive dysfunction
Insulin Resistance (IR)

Central pathogenic factor
IR → compensatory hyperinsulinemia → worsens androgen excess & inflammation
Hormonal Dysregulation

Phenotype

NO UNIQUE FEATURE

ANY TWO

Oligo / anovulation

Hyperandrogenism
Clinical and / or
Biochemical

+

POLYCYSTIC OVARY

EXCLUDING OTHER AETIOLOGIES

Rotterdam Consensus Workshop, 2003
ESHRE /ARSM 2010, Endocrine Society JCEM 2013

Screening and Diagnosis

On average 2 years delay

Avoid – overdiagnosis in adolescents

(2005) community based screening

~50% culture of silence in Sri Lanka

Kumarapeli, V et al. Am J of Epidemiology

Polycystic Ovary Syndrome (PCOS)

Life cycle approach
Psychosocial aspects
NAME CHANGE SUGGESTED

- **Multidisciplinary care pathways**
- **Consumer participation**

Prioritize clinical questions (Consumers, Primary care, Clinicians and Researchers)

- **Systematic reviews - Evidence synthesis via PICO**
  Narrative review

GRADE Recommendations

- **Revisit of International Practice Guidelines of 2018**
  NHMRC Australia Endorsement for International dissemination

Balen, 1994 & 1999

Phenotype

NO UNIQUE FEATURE

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Oligo / anovulation

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+

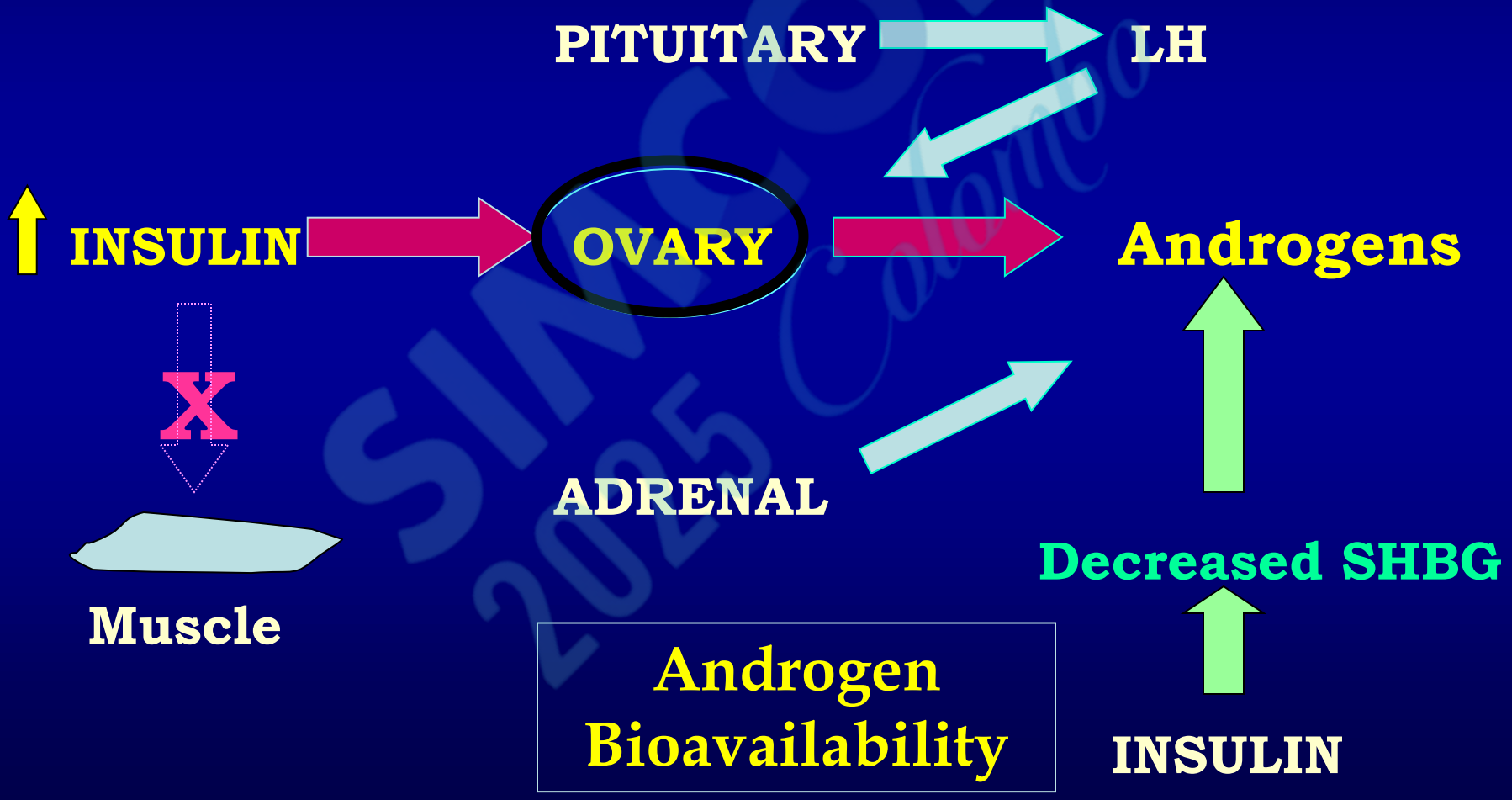
POLYCYSTIC
OVARY

- **Foll Diam 9-12 mm**
- **FNPO > 20**
- **FNPS > 10**
- **Ov Volume >10 cm^3**
- **T/A scan OV, FNSP**

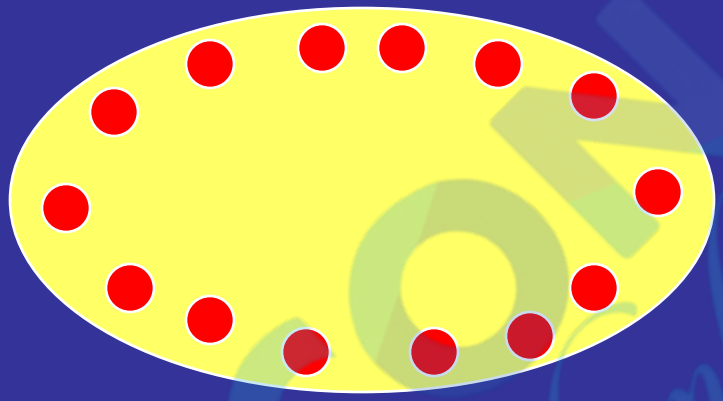
EXCLUDING OTHER AETIOLOGIES

Rotterdam Consensus Workshop, 2003
ESHRE?ARSM 2010, Endocrine Society JCEM 2013

Pathophysiology of HA PCOS : the role of Insulin Resistance (IR)



PCOS



Hyperandrogenism
Menstrual disturbances
Infertility
Obesity
Cardiovascular risks
Pre-Diabetes
NAFLD/NASH
OSA

↑ testosterone, *androstenedione*
↑ luteinising hormone
AMH
↑ *insulin, IGF-1*
↑ prolactin
disturbed lipid profile
↓ *SHBG, IGFBP-1*
Increased cytokines
IL6, TNFα,IL-1β

Clinic-based investigations

Serum FSH; LH……AMH

TSH

Prolactin

Testosterone - nmol/l (normal adult female 0.22-0.5)

17 hydroxy progesterone –(<3.6 nmol/l)

– ideally 60 min post 250 µg ACTH

Overnight dexamethasone test – negative

75g oGTT – 2h

Cholesterol >200; TG >150; HDL <55; TC/HDL

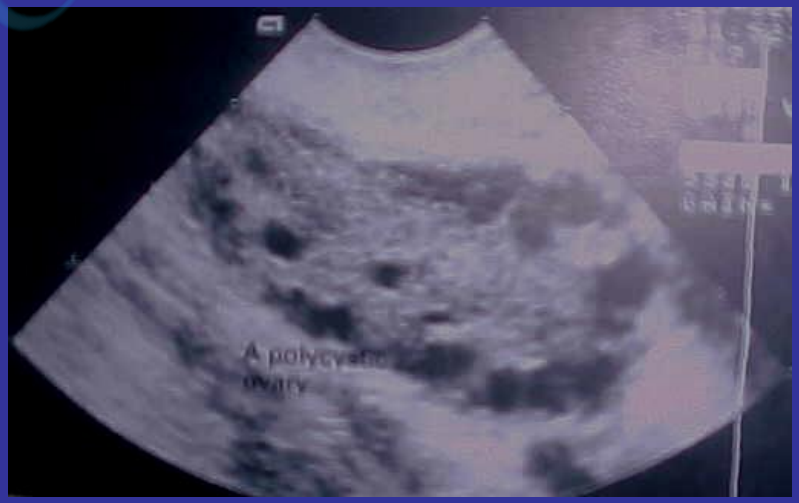
NOT FASTING INSULIN and SHBG

Eugonadotrophic

WHO Type 2

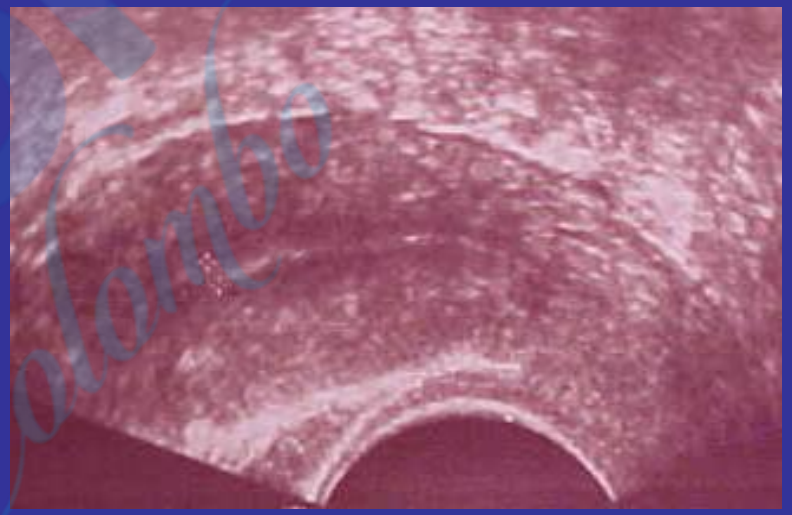
Other causes - NIL

= PCOS + MetS/IGT



Pathophysiology of HA in PCOS

Increased LH secretion
Ovarian androgen excess
Low tonic FSH production
High oestrogens



PCO – abnormal follicular growth
mid antral arrest WITH
granulosa cell degeneration
theca cell activation

PCOS as a Chronic Inflammatory Disorder

LH related high Prolactin contributes to:
anovulation
metabolic disturbance

Autoimmune Association

- Increased prevalence of autoimmune thyroid disease
- Emerging links to other autoimmune disorders
- Possible shared inflammatory pathways

In patients with irregular menses and HA
..ovarian U/S is NOT necessary to diagnose PCOS

AMH should NOT be used as a single test in diagnosing PCOS, but useful to define PCOM

PCOM - U/S needs standardization
Technical resources and observer training

When dominant follicle is present, need to rely on FNPO in the contralateral ovary

Uterine features including ET and pattern

Oligo-amenorrhoea
IRREGULAR CYCLES

Pubertal transition - first 12 months may be a normal phenomenon

1 – 3 years post menarche <21 d and > 45 d

- 3 years post menarche to perimenopause <21d and > 35d or < 8 cycles per year

FOR ADOLESCENTS AT INCREASED RISK AWAIT 8 YEARS AFTER MENARCHE AND RE-ASSESS

MEAN AGE OF MENARCHE

Hyperandrogenism

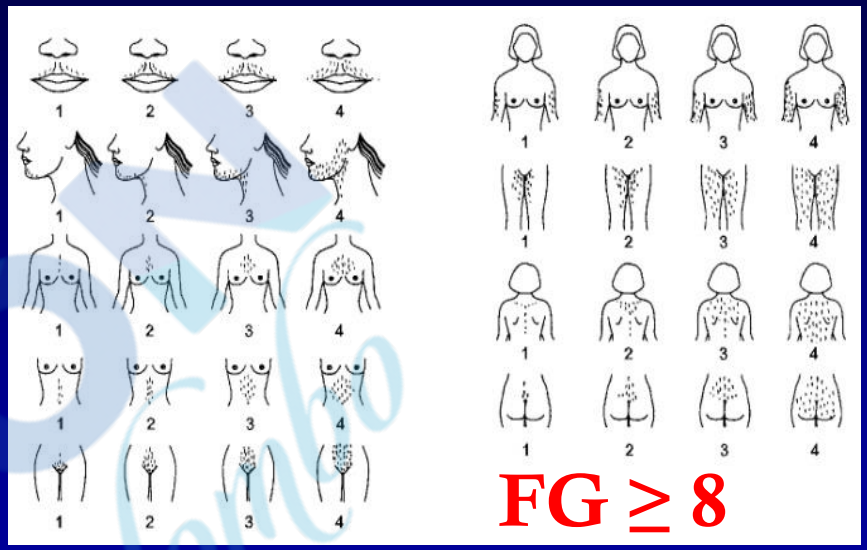
Hirsutism

Subjective (patient and physician)

Quantify Ferriman Gallwey Score

Ethnic variations

Distribution varies



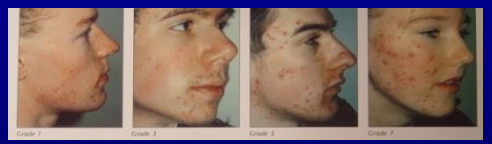
Alopecia Androgen mediated / iron deficiency

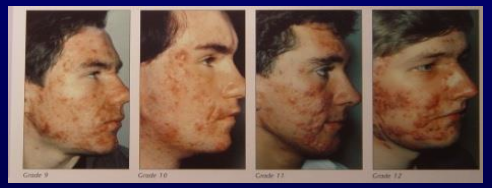
Acne 54% of women have physiological acne, 3% clinical acne

70% adolescents

Correlates poorly with hyperandrogenemia

Balen A, 2017



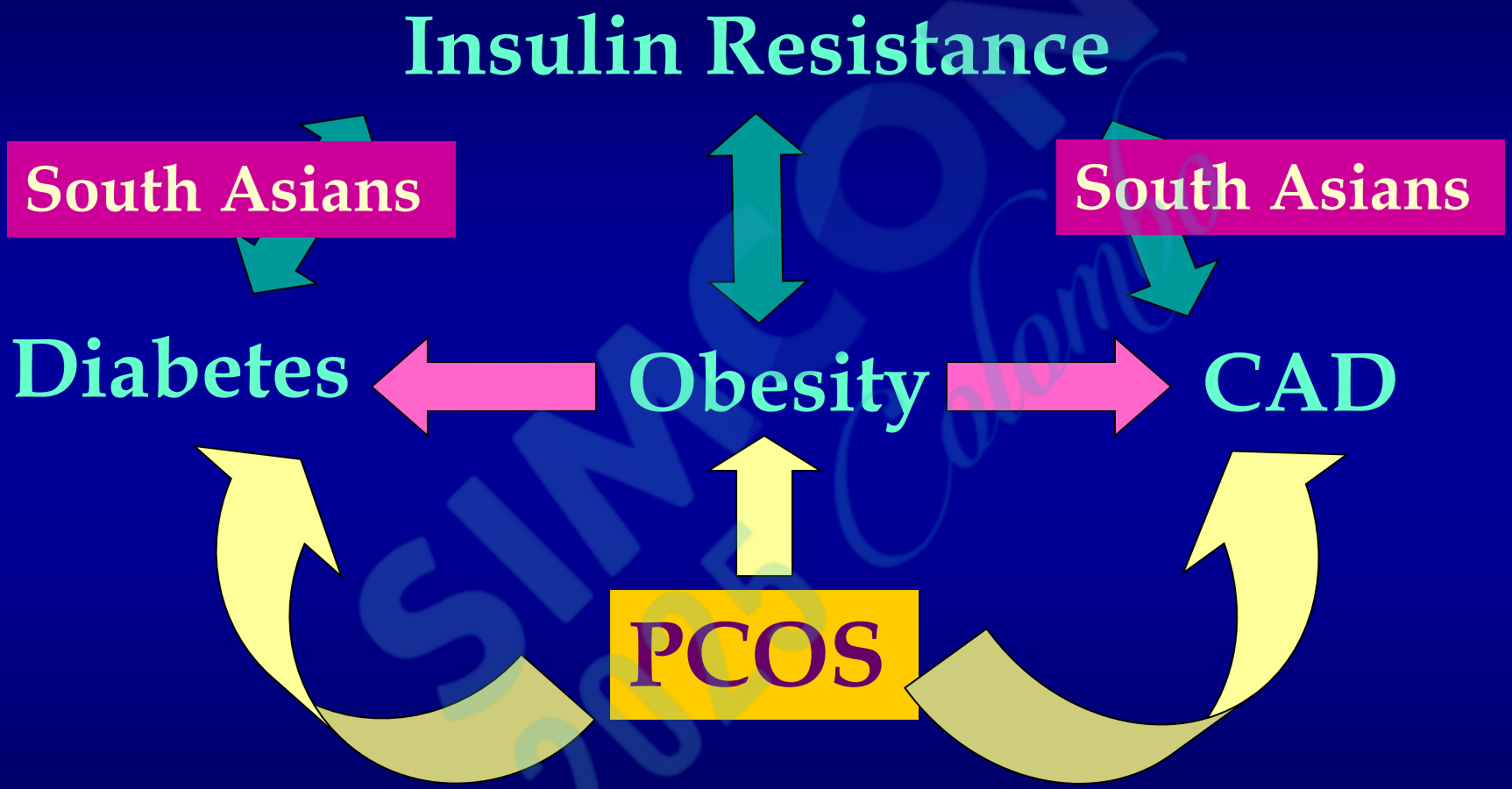


Manifestation of HA

Some with excess androgen have
no skin manifestations
seborrhea, hydradenietis, acne or alopecia
WITHOUT hirsutism

No scoring system for acne

Ethnic variations




SLNCON
2025 Colombo

Patient Education, Engagement, Empowerment

At diagnosis

- ❖ **Psycho-social and cultural impact**
- ❖ **Preferences**
  - **Educate**
  - **Reassure**
  - **Emphasize potential for risk reduction**
  - **Good reproductive potential**
  - **Some medical assistance (AVOID over-medicalization)**
  - **SELF-EMPOWERMENT**
  - **PERSONALIZE – cultural preferences**

South Asian women resident in Britain with anovular PCOS

when compared with their white Europeans :

a) Present earlier

b) develop menstrual irregularity at younger age

c) have more hirsutism & acanthosis nigricans

d) have a higher prevalence of DM in the family

e) have a significantly higher fasting insulin / IR

f) similar testosterone but significantly lower SHBG

Wijeyaratne CN, Balen AH, Barth JH et al. Clinical manifestations and insulin resistance (IR) in Polycystic Ovary Syndrome (PCOS) among South Asians and Caucasians: is there a difference? *Clinical Endocrinology 2002*

Relevance to indigenous South Asian populations

Summary

Indigenous Sri Lankans with anovular PCOS :

a) are significantly more centrally obese

b) Have greater prevalence of acanthosis nigricans

c) are significantly more insulin resistant

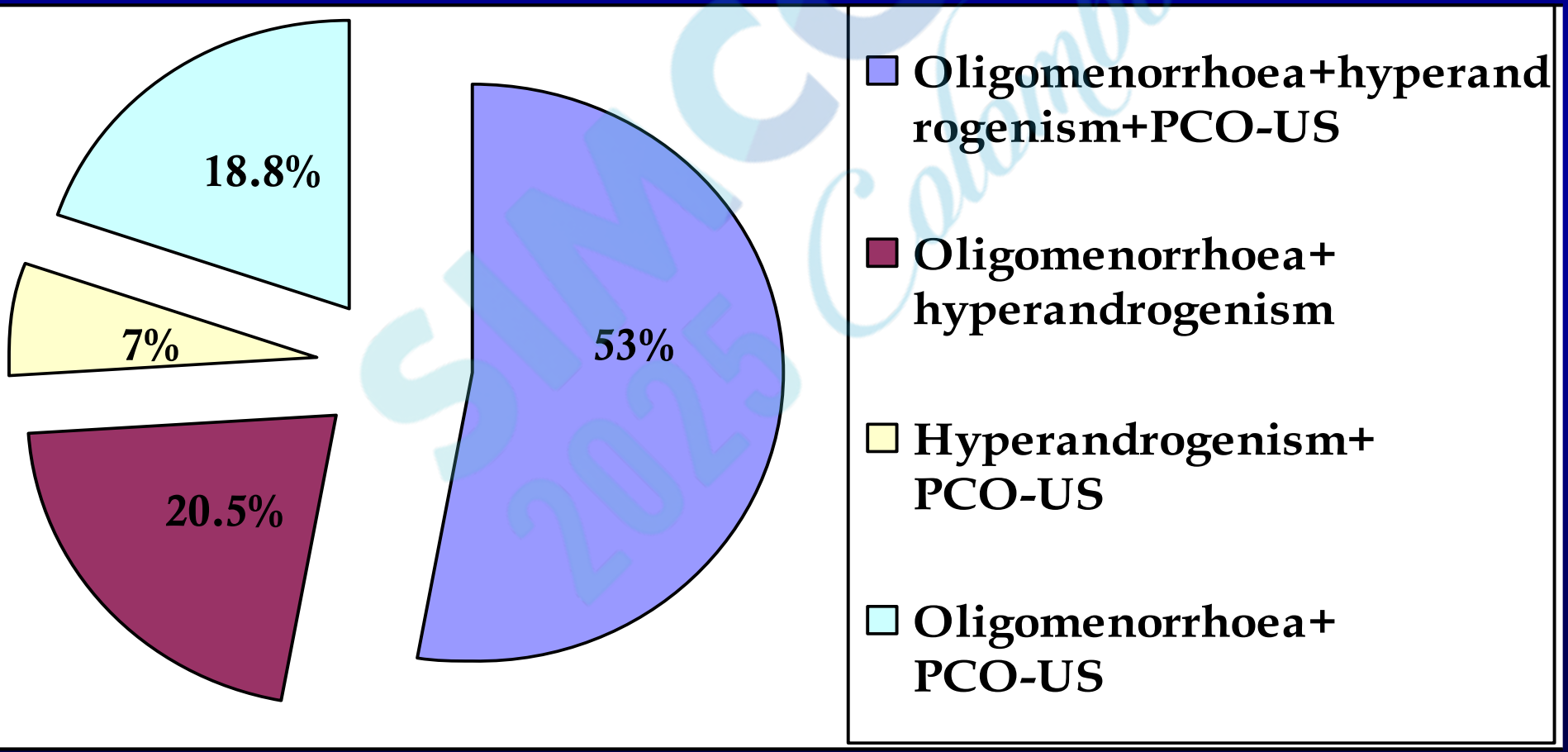
d) are significantly less hirsute

e) have significantly lower SHBG and higher FAI

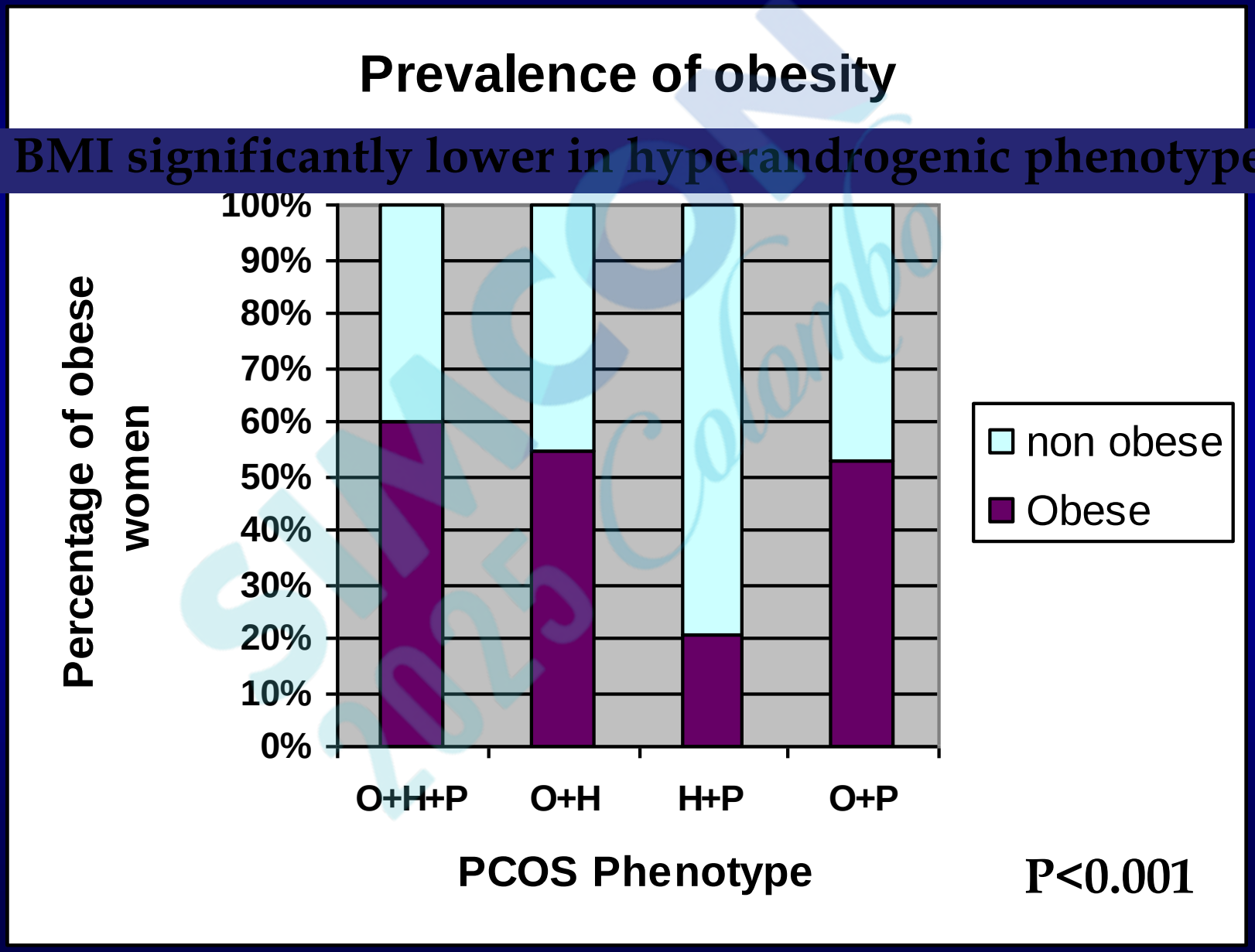
Endocrine Clinic, Colombo, Sri Lanka (n= 470)

Mean age 25 yrs; Hirsutism 70%; Median FG = 10

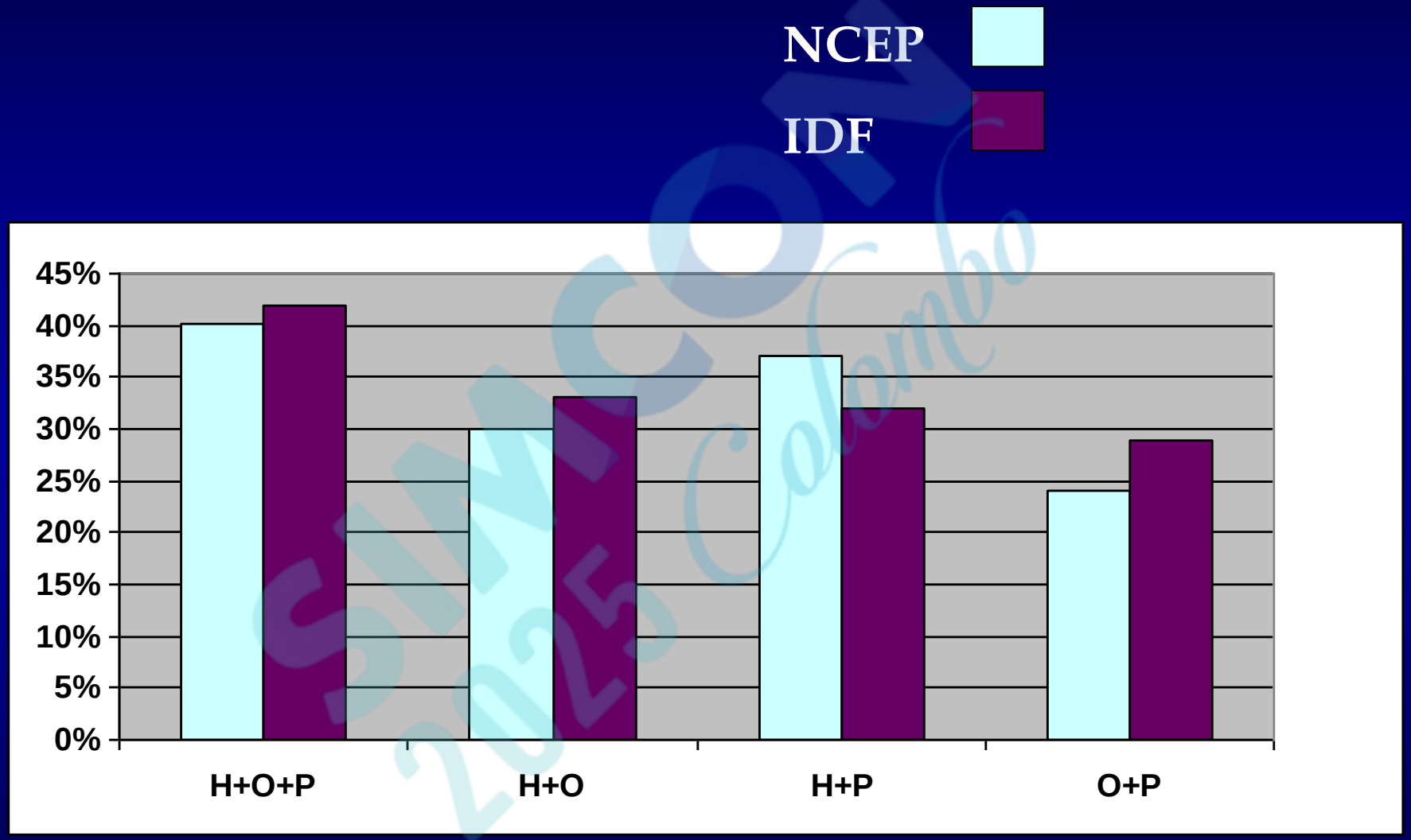
Age of onset 18 years



Obesity and phenotype in Sri Lankans (n= 470)



Metabolic Syndrome by phenotype – Sri Lankan cohort



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- Lifestyle interventions (exercise, diet and behavioural strategies) recommended for ALL
- Optimize general health, QoL, address metabolic health, body composition and weight management
- A lifelong focus on prevention of weight gain
- Key life points: adolescence, pre-marital, pre-conception, pregnancy (GDM, PIH, GWG), pre-menopausal and post menopausal
- Risk reduction of CVD (BP, DM, Lipids, CAD)
- ANY dietary composition, exercise / physical activity consistent with population guidelines
- Prevention of excess weight gain
- Be conscious of weight stigma + biopsychosocial impact

Miss SL age- 19 years

AL exam in 6 months

c/o 3 periods per year and excess facial hair with acne

Capital hair loss > frontal

Weight 93kg (+16 kg over 2 years)

Dark skin with tags on nape

Dark patches armpits, mid-sternal, knuckles, face

Hyperandrogenism +Acanthosis nigricans

Miss SL age- 19 years
AL exam in 6 months

CLINICAL CARE PATHWAY

COCP - adolescent at risk or with clear diagnosis

No clinical adv. of high dose EE2 (>30 μg) vs. low dose

General population guidelines suffice

Endometrial protection

In conjunction with cosmetic therapies, metabolic management, side effects, costs, availability

Individualize – contraindication and adverse effects
Social value systems, cultural beliefs and taboos

Miss SL age- 19 years
AL exam in 6 months

METFORMIN

To be considered in adults with BMI > 25

Adolescents – shared decision making with LSM

Address dose dependent GI side effects

Dose – increments fortnightly and Slow Release

Vitamin B12 deficiency needs addressing

Combined with COCP offers little additional benefit for those < critical BMI

Not so effective for hirsutism

Anti-obesity – pharmacology

GLP-1 receptor agonists (liraglutide, semaglutide)

Promising….off-label

In conjunction with Metformin and active LSM

Needs concurrent effective contraception

Bariatric surgery

Inositol – limited evidence of clinical benefit (complementary medicine)

Shared decision making

Anti-androgens – pharmacology

Spironolactone

In conjunction with COCP trial after a minimum of 6 months of COCP alone

In conjunction with active LSM

Needs concurrent effective contraception if unable to tolerate COCP

CPA x

Finesteride – hepatic toxicity
Flutamide – (-do-)

Fertility treatment – pharmacology

Algorithms with multidisciplinary partnerships

Reassurance

Pre-natal vitamins

Letrozole, metformin, CC and OHSS

Metformin in pregnancy

Reduction of multiple pregnancy

Guarded advice on offspring weight issues

Adverse pregnancy outcomes

High GWG

Miscarriage

GDM/HIP **PRE-PREGNANCY METABOLIC CHECK WITH 75g oGTT**

Hypertension – preeclampsia

IUGR

Pre-term delivery

C Section rates

Metformin could be considered (pre-term births)

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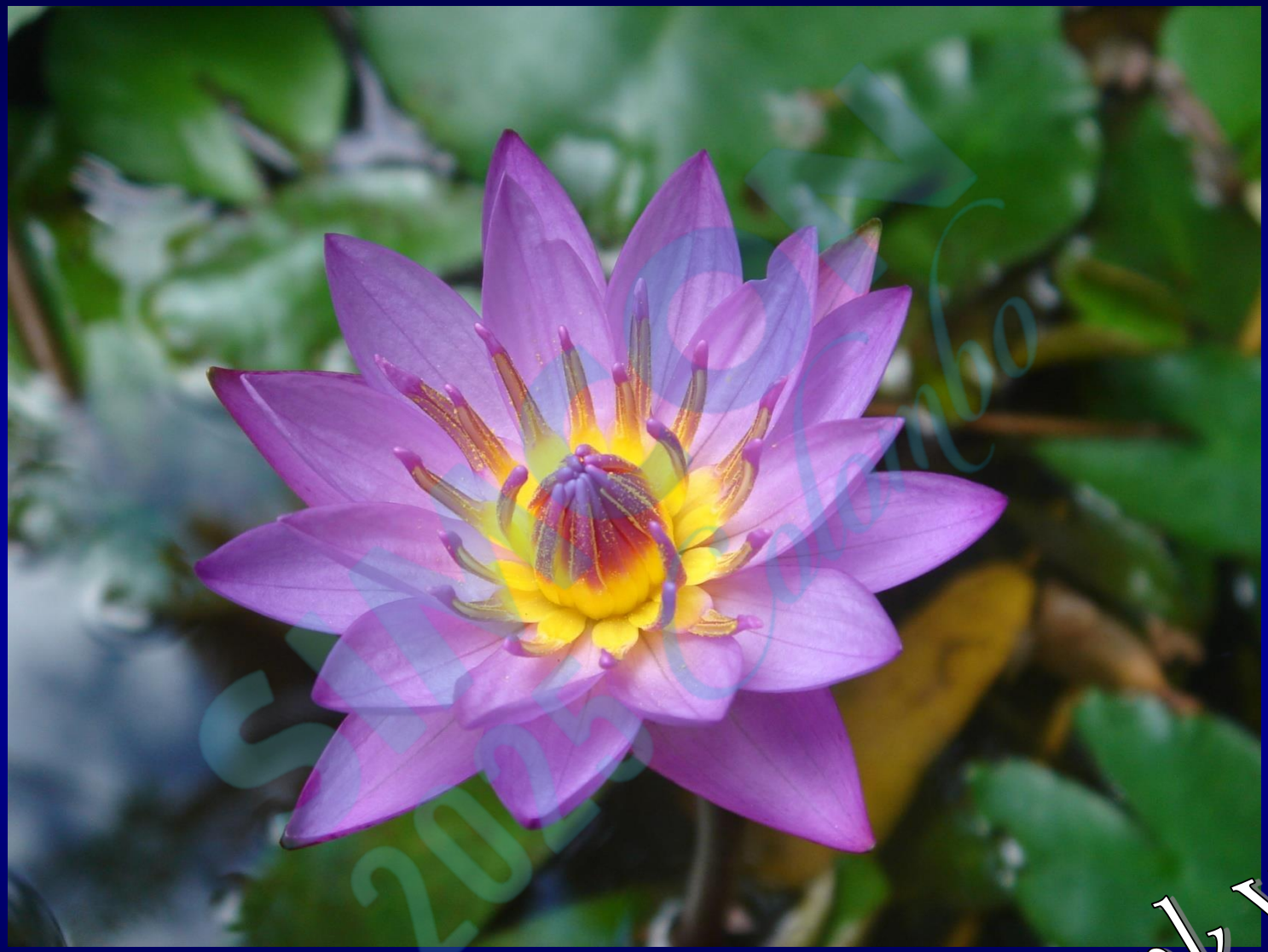
Genetics?

Polygenic risk scores

Calibration across ancestries is limited and prospective clinical utility still needs trials and diverse biobanks

Common risk loci converging on gonadotropin, androgen, and metabolic/insulin pathways

Adiposity is a causal driver of genetic risk translation to disease



Thank You